35. (new) The method of Claim 34 wherein said administering is carried out in a vascular fashion.

36. (new) The method of Claim 35 wherein said vascular administration is intravenous.

37. (new) The method of Claim 34, 35, or 36 wherein said erythropoietin is administered for the treatment of stroke.

38. (new) The method of Claim 34, 35, or 36 wherein said erythropoietin is administered at a dosage of 50,000 to 100,000 Units per administration or per day.

39. (new) The method of Claim 34, 35, or 36 wherein said erythropoietin is native erythropoietin, recombinant human erythropoietin or animal erythropoietin or a derivative thereof.

REMARKS

Applicants thank Primary Examiner DeBerry, and Supervisory Patent Examiners Kunz and Kemmerer for the courtesies extended during the interview of July 30, 2002 at the United States Patent and Trademark Office with Dr. Anthony Cerami, one of the inventors of the above-captioned application, and Frederick J. Hamble, Esq., of Kenneth S. Warren Laboratories, Inc., and Applicant's representatives Laura A. Coruzzi and Eileen E. Falvey of Pennie & Edmonds, LLP. The amendments and remarks made herein are in response to the Office Action mailed June 13, 2002 and reflect the content of the discussion and suggestions made by the Examiners during that interview.

It is noted with appreciation that the references cited in the Information Disclosure Statement originally filed on November 20, 2000, replacement copies of which were provided on May 21, 2002, have been considered, and that the Office Action dated May 8, 2002, and the rejections made therein, has been vacated.

Claims 28-39 are pending in the instant application. The claims have been amended to specify the peripheral administration of *an effective non-toxic amount* of erythropoietin.

No new matter is added by this amendment which is fully supported by the specification and claims as originally filed (*e.g.*, see Summary of the Invention at p.4, *ll.* 26-27). Claim 34, directed to the treatment of human subjects, has been rewritten in independent form and new Claims 35-39, which depend from Claim 34, parallel original Claims 29-33.

The specification has been amended to change the title of the invention to more accurately reflect the claimed subject matter, and to correct a typographical error in the Brief Description of the Figures. Applicants assert that the amendments to the specification do not introduce new matter.

1. THE CLAIMED INVENTION

During the Interview, an overview of the claimed invention, relating to methods for treating cerebral ischemia using effective, non-toxic amounts of erythropoietin ("EPO") was presented. The basis for the invention was discussed in detail. This section summarizes the highlights of this discussion.

By way of background, EPO is a glycoprotein which is essential to the process of red blood cell production, *i.e.*, erythropoiesis. Once thought to be a maturation factor, EPO is now understood to increase red blood cell production by preventing apoptosis of erythropoietic cells during their maturation process.[1] However, in order to increase an individual's red blood cell count, or hematocrit, prolonged exposure of EPO with erythropoietic cells maturing in the subject's bone marrow is required.[2]

Apart from its erythropoietic activity, the Applicants unexpectedly discovered that peripherally administered EPO is transcytosed across the blood brain barrier, becoming

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[1] EPO interacts with the EPO receptor present on immature red blood cells (CFU-E and proerythroblasts) to upregulate the Bcl2 family to block apoptosis of CFU-E and proerythrocytes, thereby increasing the production of red blood cells (see Silva *et al.*, 1999, J. Biol. Chem. 274:22165-69).

[2] Prolonged interaction of EPO with target cells of the hematopoietic system is required for erythropoietic effect *in vivo* (for a full discussion of this phenomenon see Goldwasser *et al.*, 1974, J. Biol. Chem., 249:4202-4206; IDS #DM). For example, in Grimm *et al.*, recombinant human EPO was administered to patients thrice weekly at a dosage of approximately 70-90 U/kg for more than 4 months (IDS# BC; 1990, Kidney International, 38: 480-486).

associated with cells of the central nervous system ("CNS"), such as neurons and astrocytes.[3] The Applicants have demonstrated (and others have since confirmed) that when high doses of EPO are peripherally administered to a mammal *in vivo*, the transcytosed EPO can be detected in the cerebral spinal fluid ("CSF").[4] The transcytosed EPO exerts a protective effect on such excitable cells and tissues, *i.e.*, cells and tissues which possess receptors for EPO.

Based on their discoveries, the Applicants developed methods for the peripheral administration of EPO to achieve its protective effects without a clinically significant increase in hematocrit. In one such method, asialoerythropoietin ("asialo-EPO"), which the Applicants discovered retains the protective effects of EPO but is too short-lived in the circulation to be present at a concentration adequate to cause a rise in hematocrit, can be used. In an alternative method, which is the subject matter of the present claims, EPO is peripherally administered at doses sufficient for transcytosis and protection of excitable cells and tissues (such as administering it as a bolus), yet for durations that are too short to result in a clinically significant increase in hematocrit. These dosage regimens result in fewer side effects associated with unwanted increase in hematocrit and blood viscosity, which is particularly attractive for acute treatment regimens for treatment of patients with cerebral ischemia.

2. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the claimed method of administering erythropoietin at a dosage of 50,000 to 100,000 Units per administration (or per day) lacks enablement in view of certain references cited by the Examiner which allegedly teach away from the claimed dosages. This rejection is in error and should be withdrawn for the reasons detailed below.

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[3] See application as originally filed at Example 1 at pp. 28-29 and Figure 1; Brines *et al.*, 2000, Proc. Natl. Acad. Sci. USA 97:10526-31, p. 10531

[4] *Id.*; Juul *et al.*, 2001, Society for Neuroscience Abstracts 27(1):929; and Farrell *et al.*, 2001, Blood 98(11):148b.

First, the Examiner cites Sakanaka *et al.* (1998, Proc. Natl. Acad. Sci. USA; "Sakanaka") as purportedly teaching that EPO, when administered at high concentrations, induces a rapid down-regulation of the erythropoietin receptor, resulting in failure to transmit EPO-mediated signals to the neurons. Applicants respectfully submit that the experiments presented in Sakanaka, which involve *intracranial* administration of EPO in animals, are not relevant to the methods of the claimed invention, directed to methods for *peripheral* administration of EPO. In Sakanaka, high doses of EPO were administered *directly* into the cerebral left ventrical of gerbils (Sakanaka, p.4635, col. 2, "Materials and Methods") - - a method which cannot be considered peripheral administration (see discussion in "Background of the Invention" on p.3, *ll.* 12-22 of the specification of the instant application). As first discovered by the Applicants, when such high dosages are, *instead*, administered peripherally, (defined in the specification at p.27, *ll.*19-21 to include, *e.g.*, intravenously, parenterally, or intraperitoneally), an effective amount of EPO is capable of crossing the blood-brain barrier and acts to protect the site of ischemic injury (see specification of instant application, p.4, *ll.* 7-13). For example, the experiments in Example 9 show that high doses of EPO administered peripherally cross the blood-brain barrier (see specification at pp.35-36 and Fig. 9). Example 4 of the instant application demonstrates that high doses of EPO injected *parenterally* protect animals from neural cell death in a rat model of cerebral ischemia (see specification, p.32, *l.* 25, to p.33, *l.* 5). The claimed invention requires peripheral administration of an effective non-toxic amount of EPO to provide such protection (for example, see specification, p.4, *ll.* 24-29) - - a protocol not met by the intracranial injection experiments described in Sakanaka. Therefore, the effects noted by Sakanaka cannot be extrapolated to the claimed invention.

Next, the Examiner cites Nissenson *et al.* (IDS#4 BY: Nissenson *et al.*, Ann. Int. Med. 114:402-416; referred to herein as "Nissenson")[5] and Ogden (IDS#4 CA; 1989, Sem. Nephrol. 9 (suppl. 2):12-15; referred to herein as "Ogden") which purportedly teach that patients treated with recombinant human EPO at high dosages experienced severe

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[5] On p. 4, 3rd paragraph, of the Office Action, the Nissenson article is referenced as "IDS#BZ," which is Nissenson, 1989, Sem. Nephrol. 9 (suppl. 2):25-31). However, because the textual citation referred to by the Examiner (*i.e.*, p.407, 2nd paragraph) does not appear in BZ but *does* appear in the latin publication by Nissenson, IDS #BY, Applicants have taken the Examiner's remarks as referring to BY.

complications, such as hypertension and seizures. However, Applicants assert that Nissenson and Ogden are non-analogous, and therefore, not relevant to the enablement of the claimed invention, for the following reasons.

The clinical trials reported by Nissenson and Ogden did not involve treating the patient population required by the claimed methods. None of the patients in Nissenson or Ogden are reported to have *cerebral ischemia*, as *required by the claims*. Instead, Nissenson and Ogden describe treating renal failure patients on chronic dialysis, who, as a result of their renal diseases, have anemia. The side effects reported by Nissenson and Ogden, as the Examiner even noted, *were not due to the EPO per se*, but, rather, to the rapid rise in hematocrit in this particular patient population (see Nissenson, p.407, 2nd paragraph, last sentence). As explained by Ogden, patients with renal failure have increased cardiac output. When treated with EPO, these patients experience hypertension because, despite the increases in blood viscosity and peripheral resistance, these patients do not experience a commensurate adjustment in cardiac output. In particular, Ogden explains (p.13, 2nd paragraph):[6]

> This side effect may be related to the increased cardiac output that is frequently associated with renal failure and is usually attributed to a decrease in oxygen delivery secondary to anemia and to lowered blood viscosity. Recent findings suggest that the increased BP observed in r-HuEPO-treated patients may by caused by a decrease in compensatory peripheral vasodilation without commensurate decrease in the elevated cardiac output.

In other words, the side effects observed by Ogden and Nissenson are peculiar to their patient population, *i.e.*, anemic patients on chronic renal dialysis. In contrast, the claimed methods are directed to treating patients with cerebral ischemic disease, whether or not they have anemia.

Moreover, the claimed methods require amounts and dosage regimens of EPO which are effective to gain access to the ischemic area yet are *not toxic*, *e.g.*, dosage regimens that *do not* result in a clinically significant increase in hematocrit as a consequence of the erythropoietic activity of EPO (for example, see specification at p.13, *ll.* 24-26, and Section 5.4.1, especially p.22, *ll.* 25-31, and p.23, *l.* 28, to p.24, *l.* 12). This aspect of the invention is

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6 See also Nissenson BZ at p.30, first column.

more clearly defined by the amended claims, which require the administration of effective *non-toxic* doses. As such, the dosage regimens described by Nissenson and Ogden are not analogous to the dosage regimens of the methods of the claimed invention.

In view of the foregoing, applicants submit that the rejections for lack of enablement under 35 U.S.C. § 112, first paragraph, are in error and should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 28 and 32 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. This rejection is obviated by the amended claims and remarks below.

Claim 28 has been amended to require the administration of an effective non-toxic dose (as supported by the written description throughout the instant specification, especially at p.4, *l.* 24, to p.5, *l.* 3), and thus the body of the claim relates back to the preamble.

Claim 32 is not indefinite. The claimed method provides individualized dosage amounts as Units per individual, independent of body weight. Such dosages are described at p.23, *ll.* 10-20, and are distinguishable from the dosage regimens provided as Units/kg body weight, described on p.23, *ll.* 28-34.

Thus, Applicants submit that the rejections for indefiniteness under 35 U.S.C. § 112, second paragraph, have been overcome and request their withdrawal.

4. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 28-31, 33, and 34 under 35 U.S.C. 102(b) are rejected as anticipated by Grimm *et al.* (IDS#4 BC; 1990, Kidney International, 38: 480-486; "Grimm"). The Examiner alleges that Grimm describes methods for administering erythropoietin peripherally to a mammal to treat cerebral ischemia. The basis for this rejection is in error and the rejection should be withdrawn. As discussed in detail below, Grimm does not describe methods for treating cerebral ischemia, as required by Claims 28-34 and new Claims 35-39. Instead, Grimm describes treating severe anemia in chronic hemodialysis patients.

Anticipation requires that all the elements and limitations of a claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). A prior genus which does not explicitly disclose a species does not anticipate a later claim to that species. *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988); *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1261, 9USPQ 2d 1962, 1970 (Fed. Cir. 1989); *see* Donald S. Chisum, Chisum on Patents, § 3.02[2], at 3-21-22 (2002).

Methods for treating cerebral ischemia are not disclosed in Grimm. Instead, Grimm describes the use of EPO to treat severe anemia in chronic hemodialysis patients, *i.e.*, chronic kidney dialysis patients suffering from severe anemia caused by a deficiency of erythropoietin whose anemia results in impaired exercise capacity and quality of life. According to Grimm, the patient population treated with EPO was otherwise in good clinical condition, and led normal active lives (see p.485, col. 1, *l.* 10-12). None of the patients in Grimm's study are reported to have cerebral ischema. The focus of the Grimm study is to treat the anemia using EPO to restore a sense of well being, quality of life, and working capacity to these relatively normal, active patients. In contrast, the claims of the instant invention relate to methods for treating patients with cerebral ischemic disease, whether or not they have anemia, an entirely different patient population from the patient population of the Grimm study. Thus, Grimm does not anticipate the method of the claimed invention.

Moreover, there is no recognition in Grimm of the unexpected ability of EPO to cross the blood-brain barrier, which forms the basis for the methods using high-dose regimens of the claimed invention. Rather, Grimm focuses on the treatment of anemia by administering EPO to raise the hematocrit, thereby correcting the anemia, which, according to Grimm, is the underlying cause of the brain dysfunction. As explained by Grimm, the results of the study confirm the beneficial mental effects of recombinant human EPO in these patients, and strongly suggest that the beneficial effect "is due to the partial correction of anemia and not related to other effects" (Grimm, last sentence on p.484 to top of 485; p.484, col 1, *l.* 22). In other words, Grimm teaches the use of a sufficient amount and dosage regimen of EPO to

cause an *increase* in hematocrit in these anemic patients (see p.481, Table 1A).[7] In contrast, the methods of the instant invention require treating patients with cerebral ischema, using amounts and dosage regimens of EPO sufficient to cross the blood brain barrier to achieve neuroprotective effects, yet which are not toxic - - *e.g.*, do *not* significantly cause an increase in hematocrit (see specification at p.13, *ll.*19-21 and Section 5.4.1, especially p.22, *ll.*35-31, and p.23, *l.*28 to p.24, *l.*12). Thus, Grimm does *not* anticipate the claimed methods for administering EPO to subjects with cerebral ischemia.

For all the reasons discussed above, Grimm does not disclose or suggest the claims of the instant invention. Accordingly, Applicant respectfully requests that the rejection of Claims 28-34 under 35 U.S.C. 102(b) be withdrawn.

CONCLUSIONS

Entry of the foregoing remarks into the record of the above-identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

Date August 13, 2002

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Enclosures

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[7] Grimm used low doses of EPO administered chronically, *e.g.*, 70 ± 15U/kg to 94 ± 27U/kg of EPO thrice weekly (*i.e.*, 210 to 282 U/kg per week) over a duration of 4.7 ± 1.2 months (Grimm, p.480, col 2, last paragraph and Table 1B).